Dissertation on

PREVALENCE OF CO-MORBID CONDITIONS IN RELATION TO SEVERITY OF ASTHMA

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CERTIFICATE

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CONTENTS

ABBREVIATIONS

ARIA	-	Allergic Rhinitis and Its Impact on Asthma
CI	-	Confidence Interval
FEV_1	-	Forced Expiratory Volume in One Second
GERD	-	Gastro Esophageal Reflux Disease
GINA	-	Global Initiative against Asthma
OPD	-	Out Patient Department
OR	-	Odds Ratio
PEF	-	Peak Expiratory Flow

Introduction

INTRODUCTION

Childhood Asthma has emerged perhaps as the commonest chronic medical problem treated by pediatricians all over the world. what was originally thought to be a disorder affecting only adults has emerged as a very significant problem affecting the child's life style and day to day activities including schooling, sports and recreation. The incidence of asthma is increasing alarmingly in the past few decades[1].

Because asthma is a complex and heterogenous disease with many phenotypic expressions through the course of childhood, it is challenging to characterize. First the clinical manifestations of asthma are non specific and many children wheeze during the first few years of life. But only a few of these children develop persistent wheezing and clinical asthma[2]. Approximately 60% are transient wheezes who outgrow their disease by 5 years of age.

DEFINITION OF ASTHMA

The manner in which asthma has been defined has changed significantly over time.

- In 1950's asthma was defined as a disease characterized by airflow obstruction that could resolve spontaneously or following therapy[3].

- In 1960's asthma was viewed as an episodic disease in which airflow obstruction was caused by bronchial hyper responsiveness[4].

- In 1970's the concept of preventing bronchospasm and managing disease progression was considered.

- In 1990's asthma was redefined as a chronic inflammatory disease characterized by reversible airflow obstruction and bronchial hyper responsiveness[5].

Asthma is "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular mast cells, eosinophils, T lymphocytes, macrophages, eosinophils and epithelial cells. In susceptible individuals, the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and coughing particularly at night or in the early morning. These symptoms are usually associated with widespread but variable airway obstruction that is often reversible either spontaneously or with treatment. The inflammation also causes an associated increase in the existing bronchial hyperresponsiveness to a variety of stimuli".[8]

ETIOLOGY

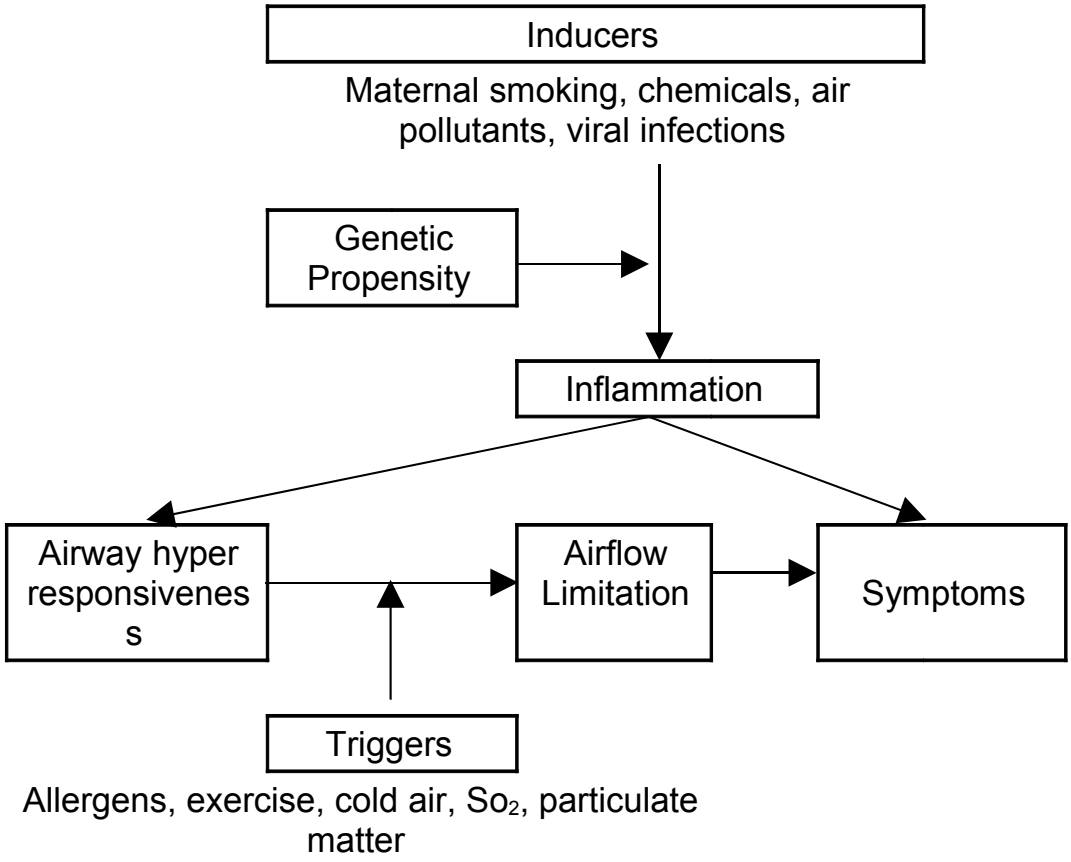
It appears due to an interplay between genetic and environmental factors.

Genetics

- More than 22 loci on 15 autosomal chromosomes have been linked to asthma.
- Asthma has been consistently linked with loci containing proallergic, proinflammatory genes (e.g. : the IL-4 gene cluster on chromosome-5).

Environment

Common viral infections like respiratory syncytial virus, allergen exposure, tobacco smoke, cold, dry air and strong odour are risk factors for airways inflammation and exacerbations of asthma.



PATHOGENESIS

The pathologic changes linked to persistent airways inflammation and hyper responsiveness underlie the chronic basis of asthma. The pathogenesis occurs in two phases (Early phase and late phase).

Early phase	Late phase
• Occurs in 30 min-2 hrs. • Mast cell degranulation and release of preformed mediators. • Histamine, LTC4, D4, E4, Platelet activating factor. • Broncho constriction	• Occurs in 6-8 hrs. • Release of cytokines and newly generated mediators. • Eosinophilic cationic protein, eosinophilic chemotactic factor. • Continued airway hyper responsiveness, mucus secretion, vasodilatation.

Airways Obstruction

Airflow obstruction in asthma is the result of numerous pathologic processes. In the small airways, airflow is regulated by smooth muscle encircling the airway lumens; broncho constriction of these bronchiolar muscular bands restricts or blocks airflow. A cellular infiltrate predominantly containing eosinophils, epithelial damage and desquamation fill into airways lumen. Excess production of mucus into airways and edema of surrounding tissues also contribute to blockage of airways.

Increased number of mast cells,

↓

Activated eosinophils, Helper T cells and
proinflammatory cytokines (eg : IL-4, IL-5, IL-13)

↓

Airway inflammation

↓

Hyper responsiveness to irritant exposures
(cold air, dry air, smoke)

↓

Remodelling
(Basement membrane thickening, collagen deposition, smooth muscle and mucus gland hypertrophy and hyperplasia)

Therefore **persistent airways inflammation and remodelling** are believed to under lie the chronic functional and pathologic abnormalities as well as the intermittent and episodic clinical manifestations of asthma[9].

DIAGNOSIS[7]

Asthma in children is suspected when they present with symptoms with or without signs, of recurrent airflow obstruction.

Symptoms suggestive of recurrent airflow obstruction

- Recurrent wheeze
- Recurrent isolated cough
- Recurrent breathlessness
- Nocturnal cough
- Tightness of chest

Signs suggestive of generalized airflow obstruction

- Generalized rhonchi
- Prolonged expiration
- Chest hyperinflation

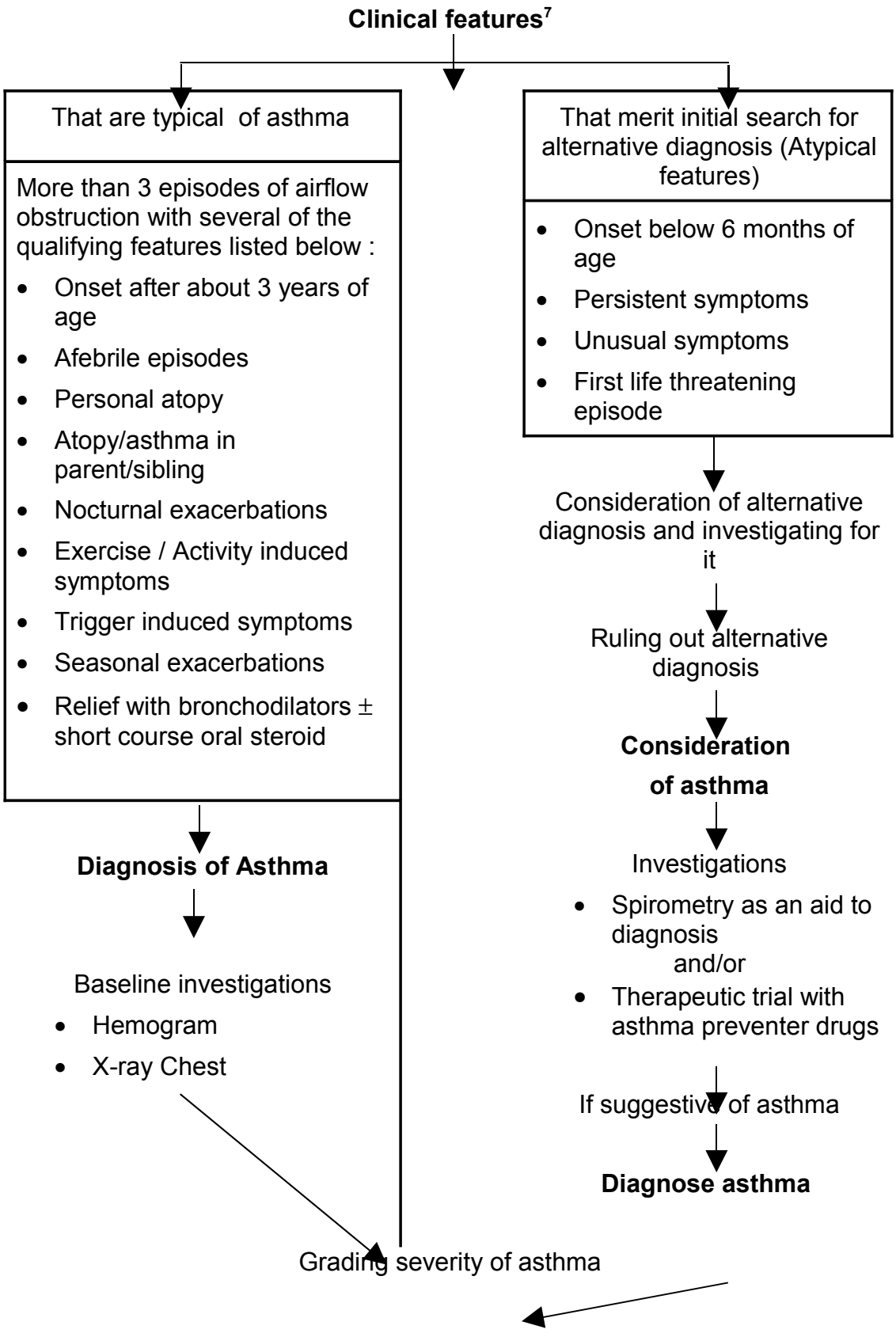
Diagnosis of asthma is made mainly by clinical means if

- Episodic symptoms of airflow obstruction (> 3 episodes are present in a year).
- Airway obstruction is reversible.
- Alternative diagnosis are excluded.

Also Asthma is considered in the following clinical situations.

- Recurrent pneumonic infiltrates in different lobes
- Recurrent ‘lower respiratory infections’

Clinical assessment to qualify the above symptoms



LUNG FUNCTION TESTS

Spirometry and peak expiratory flow monitoring are used for documenting asthma and to measure air flow and are used when physical signs of asthma were not obvious and when diagnosis of asthma is doubtful. They are also useful in monitoring asthma and in assessing efficacy of therapy.

Spirometry has a limited role in the diagnosis of asthma[7]. It is also difficult to perform in children below 6 years of age. Spirometric results reflect only the lung function on the day of testing and thus may be normal, since asthma is a dynamic condition. Spirometry can be used as an aid in doubtful cases. So children can be diagnosed as asthma, if $\geq$ 3 attacks of airflow obstruction per year with spirometry confirmation ($\geq$ 15% decrement in predicted FEV_1 during presentation or after exercise and improvement in $FEV_1 \geq$ 12% of predicted after bronchodilator therapy)[7,8,9].

Peak expiratory flow monitoring is a simple and inexpensive method and it can be used in doubtful cases of asthma and used in grading the severity of asthma.

Peak expiratory flow of personal best is done over a period of one week (best of 3 consecutive attempts) during asymptomatic periods since standard values for various population have not been identified[7]. A diurnal variation of peak expiratory flow (morning to evening variation) > 10% is abnormal.

Grading of Severity of Asthma

After having diagnosed as asthma, grading can be done according to

(1) Symptoms of air flow obstruction

(2) Night symptoms and

(3) Peak expiratory flow of personal best and diurnal variation.

Severity of asthma can be graded as :

Grade 1 : mild intermittent asthma

Grade 2 : mild persistent asthma

Grade 3 : moderate persistent asthma

Grade 4 : Severe persistent asthma

GRADES OF SEVERITY OF ASTHMA[7,9]

Grades of severity of asthma	Symptoms of airflow obstruction	Night time symptoms	Peak expiratory flow(PEF)
Grade 1 : Mild intermittent	• < once a week • Asymptomatic and normal between attacks	• < twice a month	• > 80% of personal best. • < 20% diurnal variation
Grade 2 : Mild persistent	• > once a week but < once a day	• > twice a month	• > 80% of personal best 20-30% diurnal variation
Grade 3 : Moderate persistent	• > Once a day • Attacks affect activity	• > Once a week	• > 60% to < 80% of personal best • > 30% diurnal variation
Grade 4 : Severe persistent	• Continuous • Limited physical activity	• Frequent	• < 60% of personal best • > 30% diurnal variation

DIFFERENTIAL DIAGNOSIS OF CHILDHOOD ASTHMA

The following should be considered in the differential diagnosis of asthma.

- Pneumonia
- Tuberculosis
- Croup
- Bronchiectasis
- Foreign body aspiration

- Psychogenic cough
- Vocal cord dysfunction and
- Other rare conditions like lymphoma, cystic fibrosis, allergic bronchopulmonary aspergillosis, ciliary dyskinesia, poly arteritis nodosa should be identified and excluded with the help of basic investigations, CT Scan chest and flexible fibro optic bronchoscopy.

IMPACT OF SEVERITY

Recurrent exacerbations are a major cause of morbidity and medical expenditure in patients with asthma. As the health care impacts of asthma continues to increase, it becomes important to identify factors that could have an impact on asthma severity and recurrent exacerbations.[9,10,11,12]

After ruling out alternative diagnoses (eg. Congenital heart disease, tuberculosis, chronic suppurative lung diseases), the cause for deterioration of asthma could be

1) Poor compliance (**Adherence**)
2) Incorrect **dose**, inappropriate **device**, poor **delivery**
3) **Trigger** avoidance
4) Concurrent **co-morbid** conditions.

Adherence[7]

- Poor compliance in the form of misunderstanding the need for preventer medication.
- Difficulty in delivering the inhaled drugs to young children.
- Fear of side effects.
- Inappropriate expectations of cure rather than control.

Dose, Device and Delivery

This could be due to incorrect dosing of drugs (eg : school timings) or inadequate dose for the severity grade, inappropriate device, broken spacer; Empty MDI should be checked and replaced. Delivery of medication could be poor if short quick breaths, frivolous child, MDI used directly with poor co-ordination[7].

Avoiding triggers is important, as it is a frequent cause of asthma exacerbation.

After excluding these correctable issues, it becomes important to identify the **concurrent co – morbid conditions** associated with recurrent exacerbations of asthma. Recent studies report that co – morbid conditions like allergic rhinitis, sinusitis, gastro esophageal reflux disease do play a significant role in determining the severity and morbidity of asthma[9 -14]. Rhinitis, sinusitis and gastroesophageal reflex commonly accompany asthma and can worsen disease severity. Effective management of these comorbid conditions can often improve

asthma symptoms and disease severity so that less medication is needed to achieve good asthma control.

Since the Institute of child health register a number of children with asthma and have all the specialities like pulmonology, otorhinology and gastroenterology in a close working condition the study will definitely throw more light on the subject.

ALLERGIC RHINITIS

Allergic rhinitis is recognized as a major chronic respiratory disease due to its high prevalence, impact on quality of life and associated co- morbidities, which includes bronchial asthma and allergic conjunctivitis[17]. Allergic rhinitis is commonly associated with bronchial asthma and rhinitis represents an independent risk factor for the development of asthma[13,43.]

How Allergic rhinitis affects asthma[27]?

Rhinitis and asthma are two manifestations of allergic respiratory disease. In allergic rhinitis and asthma, pathogenic events are triggered by exposure to aeroallergens. The histology of these diseases shows chronic, eosinophilic inflammation along with an increase in lymphocytes, plasma cells, and mast cells. The stroma in the nose and bronchus is typically edematous. Rather than suggesting

that the nose influences the lungs, this theory merely states that rhinitis and asthma represent global allergic involvement of the airways.

The various mechanisms by which allergic rhinitis affects asthma are

1. Nasal bronchial reflex
2. Post nasal drip
3. Increased mouth breathing
4. Systemic absorption of inflammatory mediators

1. Nasal Bronchial reflex

It appears to be a neurally mediated bronchospasm. Several studies have shown to prove this mechanism[25]. It has also been postulated that a nasal allergic reaction might result in an alteration in bronchial responsiveness. It has been recently re-evaluated that the possibility of a neural connection between the upper and lower airway, using cold and dry air caused an immediate and profound increase in pulmonary resistance that was prevented by topical nasal anesthesia and cholinergic blockade induced by inhalation of ipratroprium bromide[19]. Several studies strongly suggest the presence of a reflex involving irritant receptors in the upper airway (afferent limb) and cholinergic nerves in the lower airway (efferent limb)[20].

2. Post Nasal drip

Post – nasal drip triggers episodes of coughing and wheezing. Many studies have shown the possibility of aspiration of nasal secretions and also demonstrated that the substances placed in the upper respiratory tract could later be recovered from the tracheo bronchial tree[21,22].

3. Increased mouth breathing

Increased mouth breathing due to nasal obstruction by tissue swelling & secretions causes exercise induced bronchospasm. It had been showed that mouth breathing associated with nasal obstruction results in worsening of exercise induced bronchospasm, whereas exclusive nasal breathing significantly reduces asthma following exercise. Improvements in asthma associated with nasal breathing may be a result of superior humidification and warming of inspired air before it reaches the lower airways.

Similarly it would be expected that airborne allergens and pollutants also would be less likely to enter the lungs during periods of normal nasal function.

4. Systemic absorption of inflammatory mediators

Allergic mediators (eg : histamine, leukotriene C4, Platelet activating factor) infiltrate into the nasal mucosa during allergic

reactions. Absorption of these factors in to the systemic circulation could result in triggering of an episode.

Many studies has shown that treatment of rhinitis may result in improvement of asthma symptoms, lower airway caliber and bronchial hyper responsiveness and suggest that nasal disease contributes to the pathophysiology of asthma.

Diagnosis

For clinicians treating patients with nasal symptoms, the diagnosis of allergic rhinitis is often done by

(1) A careful history

(2) Supportive data including a suggestive nasal examination and

(3) Nasal cytology[27,31]

- History of afebrile episodes of paroxysmal sneezing, nasal obstruction, itching and rhinorrhoea (Two or more symptoms on most of the days in a year)[13].

- Findings on anterior rhinoscopy may show clear nasal discharge, oedematous pale, grayish mucosa. Reddish mucosa and purulent discharge favours infective etiology.

- Nasal cytology : Nasal secretion from nasal mucosa taken by a cotton bud is smeared and dried and viewed after adding Hansel's stain[9,36,38]. The presence of eosinophil count more than 4% (in adults >10%) is suggestive of nasal allergy[9]. It is more sensitive than peripheral blood eosinophilia. The presence of neutrophils suggests an infective etiology.

Differential Diagnosis of Rhinitis

	Eosinophilic Allergic	**Eosinophilic Non-Allergic**	**Neutrophilic**	**Vasomotor**
Clinical Findings	Typically during childhood, sneezing, nasal pruritus, clear rhinorrhea, episodic or perennial. Triggers are often obvious (e.g., dust mites, animals, pollens)	Adulthood; early, severe obstruction; anosmia; polyps common; perennial symptoms Often aspirin-sensitive, frequent asthma and sinus disease	Any age, purulent secretions, sinus tenderness, nocturnal cough, appearance most common during fall and winter. Infection typical, can be caused by irritation (e.g., cigarette or wood smoke)	Adulthood, rare in children, congestion, minimal rhinorrhea, variable presentation Can be hormonal (e.g., thyroid disease, pregnancy)
Nasal cytology	Eosinophils ± Neutrophils	Eosinophils ± Neutrophils	Neutrophils often with intracellular bacteria	Unremarkable generally

The patients with allergic rhinitis also frequently have allergic shiners (Dark, swollen infraorbitial tissue) and allergic salute (transverse crease across the nasal bridge).

SINUSITIS

The para nasal sinuses consist of four pairs of air filled cavities in the skull (frontal, maxillary, ethmoidal and sphenoid sinuses) Maxillary sinus is the commonest sinus involved followed by frontal sinus and ethmoid sinus. Since ethmoid and maxillary sinus are present even at birth and about 5-10% of children in normal population suffer from sinusitis, sinusitis as a co-morbid condition can be considered at very early age. In sinusitis impaired nasal functions increases post nasal drip and irritant burden on the lower airways which can exacerbate asthma symptoms[15].

The term rhinosinusitis more accurately reflect the inflammatory process that extends from sinuses to nasal mucosa causing symptoms of nasal obstruction and nasal discharge both prominent feature of sinusitis[27]. Sino pulmonary reflex is neurally mediated pharyngobronchial reflex that is activated by cellular inflammatory products acting directly on afferent nerve endings in the sinuses, thereby triggering bronchial hyper responsiveness[26,33]**.** Also spread of inflammatory mediators and nasal congestion leading to mouth breathing leads to bronchial hyper responsiveness. Asthma diminishes when co-existent sinusitis is maximally treated[18,32,44]. However bacteria causing sinusitis have also been linked to asthma exacerbations[41].

Diagnosis of sinusitis

Sinusitis is diagnosed based on

(1) Clinical symptoms

(2) Objective findings on nasal scopy and

(3) Radio imaging[10,17]

a. X-ray Water's view, Caldwel Luc's view

b. CT Scan – Sinuses

Clinical Symptoms

Major factors

- Facial pain on pressure or headache
- Nasal obstruction
- Nasal purulence or discharge
- Hyposmia or Anosmia
- Persistence of upper respiratory tract infection for more than 7-10 days.

Minor Factors

- ❖ Fever
- ❖ Halitosis
- ❖ Dental Pain

Patient with 2 major factors or one major and 2 minor factors will be subjected to nasal scopy and X-ray Water's view (Occipital – mental view)[40].

X-ray Water's view (occipital – mental view)

More than 4-6mm maxillary sinus mucosal edema or complete opacification or air fluid level is suggestive of sinusitis. CT – scan sinuses will be taken for doubtful cases. X-ray Water's view cannot match the exquisite details of sinuses provided by CT scan. Yet x-ray remains the imaging of choice in many places where financial constraints limit the use of C.T. scan.[30]

GASTRO ESOPHAGEAL REFLUX DISEASE

Gastro esophageal reflux disease can be a confounding factor in the control of asthma.[19,26,23,27] Not only are the asthmatic patients more likely to have GERD than the general population, GERD is now recognized as a potential trigger in many cases of severe asthma.[42,45 -

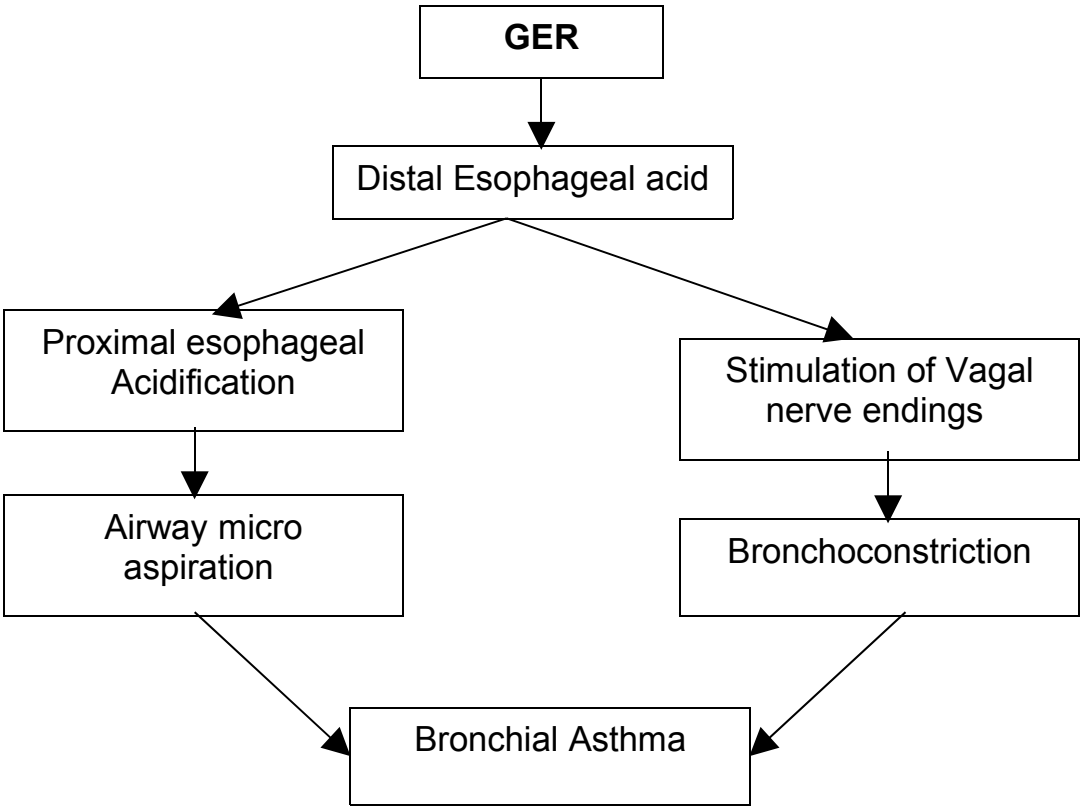
Asthmatics who may be particularly likely to have GERD as a provocative factor are those with symptoms of reflux disease, those with refractory or steroid dependent asthma and those with nocturnal worsening.

How GER exacerbates Asthma?

These following are the postulated mechanisms explaining gastro esophageal reflux leading on to asthma.[9,23,34]

- Aspiration of refluxed gastric contents (micro and macro aspiration) and
- Reflex broncho constriction.
- Further more, pulmonary hyperinflation contributes to diaphragmatic dysfunction; Bronchoconstriction results in an increase in negative pleural pressure, which effects a change in the pressure gradient between thorax and the abdomen.
- And also frequent use of bronchodilating medications may contribute to a decrease in lower esophageal sphincter tone[48].

Studies have shown that effective treatment of GERD results in decline in the number of exacerbations and will reduce the need for preventer medications.



Diagnosis of GERD

GERD can be diagnosed when the patients have

a) Typical history of symptoms

b) Barium esophagogram with fluoroscopy

c) Upper Gastro intestinal endoscopy

Clinical features suggest typical history of esophageal symptoms, chronic symptoms of acid regurgitation or heart burn and reported use of drugs for the symptoms[14].

Demonstration of reflux of barium into esophagus during a barium swallow procedure under fluoroscopic guidance is a useful tool.

Endoscopy will show hiatus hernia or patulous lower esophageal sphincter (both in anteroflux and retroflux movement) or findings suggestive of esophagitis. Even though 24 hr pH monitoring is the gold- standard for the diagnosis of GER, it is not feasible in our setup.

Review of Literature

REVIEW OF LITERATURE

Aimee Liou, MD, Daniel. L et al., at Washington university school of medicine studied 149 patients and showed certain contributing factors like allergic rhinitis, chronic sinusitis were independently associated with more severe asthma among 14 factors studied.[14]

Bresciani M. et al., in France in July 2002 -Jan 2001 studied 70 patients (Descriptive study) with 35 patients of severe steroid dependant asthma as cases and 35 controls of mild to moderate asthma and showed greater frequency of rhino sinusitis in patients with severe steroid dependent asthma than the control group.[15]

Corren J.Manning BE, et al., at Allergy research foundation, Los angels (J allergy clin. Immunol 2004 Mar;113 (3) 415 – 9) studied in a case - control study whether treatment with intranasal corticosteroids and or second – generation antihistamines is associated with changes in rates of asthma exacerbations resulting in emergency room visits and or hospitalization in patients with asthma and allergic rhinitis. They concluded in patients with asthma, treatment of concomitant allergic rhinitis was associated with significant reduction in risk of emergency room visits and hospitalization for asthma.[17]

Tosco M.A., Cosentino C, et al., at university of Genoa, Italy, Studied 18 children with moderate asthma (5-12yrs) poorly controlled

by high doses of inhaled corticosteroids and chronic rhinosinusitis were evaluated for symptoms, spirometry, and inflammation at base line, after treatment and month after suspension of treatment. They observed that treatment of chronic rhinosinusitis is able to improve symptoms and respiratory function in asthmatic children, reducing inflammatory cells and reversing the cytokine pattern from a Th2 toward a T profile.[18]

Richard S.Irwin, Fredrick J.et, al., CHEST June 1993 studied difficult to control asthma : contributing factors and outcome of a systematic management protocol. They formulated a systematic management protocol.[11]

A. Ten Brinke, J.T. Schmidt, et.al., at Department of clinical Epidemiology and Biostastics, Amsterdam and Department of pulmonary diseases, the Netherlands, studied “Risk factors of frequent exacerbations in difficult to treat asthma.” 13 clinical and environmental factors potentially associated with recurrent exacerbations in 136 patients with difficult to treat asthma. Factors significantly associated include severe nasal sinus disease (adjusted OR 3.7), Gastroesophageal reflux (OR 4.9), RRTI (OR 6.9), psychological dysfunctioning (OR 10.8) and obstructive sleep apnoea (OR 3.4). Severe chronic sinus disease and psychology associated factors (adjusted OR 5.5. & 11.7 respectively) were the only

independantly associated factors. In conclusion, the results showed that recurrent exacerbations in asthma are associated with specific co-morbid factors that are easy to detect and are treatable and therapeutic interventions aimed at correcting these factors are likely to reduce morbidity and medical expenditure.[12]

Bochenska et al., in Polland in 2004, studied 208 patients (Descriptive study) in adults with asthma and found that gastro esophageal reflux is found in 86.9% of severe asthma, 62.2% of moderate asthma, and 48.6% of mild asthma suggesting greater prevalence of reflux symptoms in severe asthma.[31]

Salvin, R.G. et. al., should the relationship of nasal disease and sinusitis to bronchial asthma and showed the positive effect of treatment of sinusitis and rhinitis in asthma in both children and adults.[24]

Huang JL. Et al., in his study evaluated 375 patients with childhood asthma between 5-15 years of age. Abnormal water's radiograph were found in 205 patients (54.7%) which include mucosal wall thickening greater then 6mm 67.3%, complete opacification 22.9% and air fluid levels 9.8%. All patients were treated with antibiotics for 3-6 weeks. In conclusion he found out that sinusitis in children may be an aggravating factor for chronic reactive lower airway disease. Optimal treatment may decrease the need of asthmatic medication[50].

Ferrante M.E. et al., in his paper presented data on the Prevalence of sinusitis in asthmatic patients and its impact on asthma. They studied 120 children with asthma and in most of them the severity of asthma was mild (74%). Sinusitis was observed in 52 patients (43.3%) and the maxillary sinus was involved in 36 asthmatics. He did not find any statistical difference between asthmatic with or without sinusitis with regard to severity of asthma, basal lung function and bronchial hyper responsiveness. He suggest that antibiotic therapy for sinusitis should be given only to asthmatic with worsening respiratory symptoms and obvious signs of chronic sinusitis[51].

Krajewski, Z. et al., in his analysis of prevalence of sinusitis in 558 children (3-6 years) old with various pulmonary disease observed that in a group of 148 asthmatic children 53 (37.3%) had sinusitis. In another group of 91 children with other atopic diseases, sinusitis was observed in 18 (19.8%) children. But in a group of 325 children with other non atopic pulmonary disease, sinusitis was found only in 19 (5.9%) children. A correlation between the severity of asthma and prevalence of sinusitis was found[52].

Marney SR. Jr.[53] in his article mentioned that the association between asthma and Sinusitis was recognized a century ago. Because

the mechanism relating sinusitis to asthma is not known he proposes the following theories.

1. Aspiration of infected sinus secretion into the lungs during sleep.

2. Enhanced vagal stimulation in the infected sinus producing direct bronchospasm.

3. Bronchospasm from excessive air way drying due to mouth breathing.

4. Production in the infected sinus of cytokines and broncho constrictive mediators.

Buscino L et al., at california university in 2001 studied in eighty children with asthma between age group of 4 and 14 years, about the prevalence of chronic sinusitis. He observed that among 80 patients 55 had sinusitis and after treatment for sinusitis, 34 had improvement of sinusitis and 20 out of 55 had decrease in severity of asthma. He concluded that owing to high prevalence of sinusitis in children with bronchial asthma, these children should be investigated and treated for sinusitis[32].

Harding S.M. et al., in recent studies supported the importance of GERD in which dosage titration of omeprazole used to confirm

complete control of acid reflux based on Ph probe testing and patients were treated for atleast 3 months. In this study 27% of patients required treatment with > 20 mg per day of omeprazole, but overall a significant improvement in asthma was achieved compared to earlier studies which were not nearly as convincing.[23]

JL Mathew, M Singh at department of pediatrics, post graduate institute of medical education, Chandigarh along with S.K. mittal at division of gasteroenterology, department of pediatrics, Maulana azad medical college, New Delhi analyzed from numerous studies a cause and effect relationship between GOR and bronchial asthma in form of evidence suggesting / against a link and concluded that

- There is a higher prevalence of GOR among patients with asthma than in general population.
- Treatment of GOR improves reflux symptoms, but fails to result in objective improvement of asthma or decrease in asthma medication in the majority of treated patients.
- There is no proven “Cause and effect” relationship between asthma and GOR as yet.[35]

Pfister et al., compared A-mode ultra sonography and standard radiography as routine screening procedure in the diagnostic work up of bronchial asthma patients having sinusitis. They took computerized

tomography as gold standard compared with results of tomography plain view radiography gave a specificity of 86.7% and for sensitivity of 52.2% for the maxillary sinus. In contrast A. mode ultra sonography demonstrated a sensitivity of 70% but a specificity of 20%. They concluded that A- mode ultrasonography is not suitable for initial screening of these patients. For routine screening for patients with asthma, the conventional water's view radiography should be used in conjunction with direct visualization of the osteomeatal area by Rhinoscopy. This combination provides information about degree of mucosal hyperplasia as well as mucosal inflammation.[30]

Rachelefsky et al., Prospectively identified 48 children aged 4 – 13 yrs who had daily coughing and wheezing for alteast 3 months, abnormal sinus radiograph and evidence of airway obstruction on pulmonary function test. These children were treated with 2 to 5 weeks of antibiotics. Post treatment evaluation revealed substantial improvement in upper and lower respiratory symptom, reduced use of bronchodilators and improved radiographic appearance of the sinuses. They suggest that children with chronic lower respiratory symptoms that are refractory to usual asthma therapy may be at increased risk of having concomitant sinusitis and this may contribute to the production of both upper and lower respiratory symptoms.[25]

Daniel. L. et al, in June 1999 in a retrospective study with stepwise logistic regression in 149 patients of more than 18 yrs age studied the prevalence of contributive factors of asthma

- Rhinitis 69.9%
- Chronic Sinusitis 42.3%
- GERD 28.2%
- Vocal cord dysfunction 7.4%
- Dust mite allergy 44.7%

and concluded patients with moderate/ severe asthma had a greater prevalence of contributive factors. Also GERD and sinusitis were independently associated with more severe asthma.[14]

Flores. F et al., at spain between July 2000 to July 2001 studied the prevalence of Gastro esophageal reflux disease in children with moderate persistent asthma in Group I (1-5 years), Group 2 (6-10 years) and Group 3 (11-16 years) and observed the prevalence among Group I & II was < 0.001 and prevalence among G I & III was < 0.001 and prevalence among Group II & III was not significant. He concluded that the prevalence of Gastro esophageal reflux was high in children with asthma suggesting that asthmatic children to be suspected for GERD[34].

Vikram Khoshoo, MD, et al., evaluated 46 children with moderate persistent asthma in the age group of 5 to 10.5 years about the asthma outcome before and after treatment of Gastroesophageal reflux of the 2% patients (59%) who had evidence of Gastro esophageal reflux disease, 18 patients under went medical treatment and 9 patients surgical treatment. Of the 19 patients with normal pH study findings, 8 patients underwent empiric medical anti-GER treatment was instituted with GER disease ($P<0.05$). Two patients (25%) without evidence of GER disease showed significant reduction in need for asthma medication after anti GER treatment, but none of the patients without GERD and no Gastro esophageal treatment showed any significant reduction in need for asthma medication[49].

Study Justification

STUDY JUSTIFICATION

- One of the long term aims of asthma management is to prevent exacerbations. This requires a better understanding of co-morbid conditions that contribute to the development of severe exacerbations.

- There are studies in adults suggesting conditions like allergic rhinitis, sinusitis & Gastro esophageal reflux are comorbid conditions of asthma.

- Studies regarding the prevalence of these comorbid conditions are minimal and lacking in Indian children.

- So it has been planned to assess the presence of these specific co-morbid conditions considered contributive to asthma exacerbations in our set up of population seen in specialized asthma clinic and

- To determine the relative distribution of co-morbid conditions in each category such as

    - Mild intermittent asthma,

    - Mild persistent asthma,

- Moderate persistent asthma and
- Severe persistent asthma, implicating co-morbid factors could contribute to the severity of the disease.

- So that children with asthma, particularly severe and difficult to control asthma may be subjected for investigation of these co-morbid conditions and to achieve adequate control of asthma after treatment of these co-morbid conditions.

Aim of the Study

AIM OF THE STUDY

1. To assess the prevalence of specific co-morbid conditions like

   (a) Allergic rhinitis,

   (b) Sinusitis and

   (c) Gastroesophageal reflux disease in children with asthma

2. Association of these conditions in relation to severity of asthma.

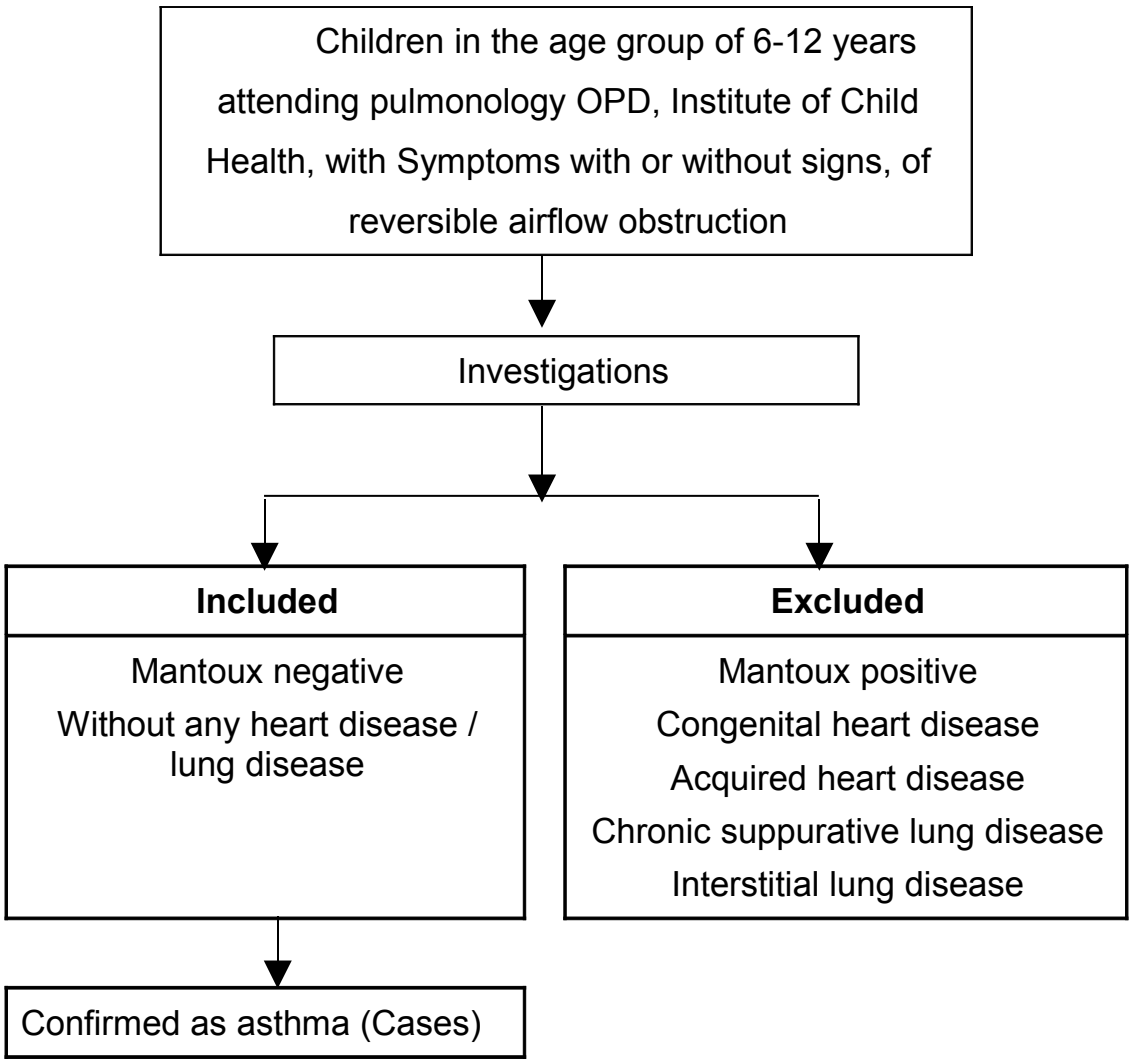
Methodology

METHODOLOGY

Study design	:	Descriptive Study
Study Place	:	Institute of Child Health and Hospital for Children Madras Medical College Chennai.
Study Period	:	February 2005 to August 2006
Study population		
Cases	:	Children in the age group of 6 to 12 years attending the Asthma clinic, Department of Pulmonology, Institute of Child Health, with symptoms with or without signs, of reversible air flow obstruction were selected. Diagnosis of asthma in them was confirmed.
Inclusion Criteria	:	Children with asthma in the age group of 6-12 years

Exclusion Criteria : Children with asthma with

- Congenital heart disease
- Acquired heart disease
- Mantoux positivity
- Chronic suppurative lung diseases.



Controls : Children without asthma in age group 6-12 years

Sample Size : 159 cases and 318 controls

Manoeuvre

MANOEUVRE

Children diagnosed as asthma were graded as

- Mild intermittent (Grade1)
- Mild persistent (Grade2)
- Moderate persistent (Grade –3) and
- Severe persistent (Grade 4), as per Asthma By Consensus (ABC) by IAP respiratory chapter; updated December 2003.

Children with asthma and controls were subjected to investigations - haemoglobin, total count, differential count, chest xray, Peak expiratory flow and spirometry. Spirometry was also taken during exacerbation.

A data entry form with a fixed questionnaire is used to evaluate co-morbid conditions like allergic rhinitis, sinusitis, GERD in cases as well as in controls.

Details of the study and procedures were informed to parents of all the children and consent obtained. Consent was also obtained from the institution.

Cases and controls with typical history of symptoms of allergic rhinitis (afebrile episodes of paroxysmal sneezing, nasal obstruction, itching and rhinorrhoea – two or more symptoms on most of the days in a year) were subjected to

(1) Anterior rhinoscopy and
(2) Nasal mucosal smear for eosinophils.

Anterior rhinoscopy in children with allergic rhinitis showed oedematous pale mucosa and clear nasal discharge. Those who had structural defects (deviated nasal septum) were excluded from diagnosing allergic rhinitis. The smear from nasal mucosa in all these cases showed eosinophil count of more than 4%[5].

Sinusitis was diagnosed based on history of symptoms (two major factors or one major and two minor factors) with

(1) Objective findings on Nasal scopy,
(2) X-ray Water's view (Occipitio - Mental View) and
(3) CT will be taken for doubtful cases.

The Nasal scopy findings revealed reddish inflamed mucosa with purulent discharge. Those with history of symptoms but with normal X-ray Water's view were excluded from the study. For doubtful cases with persistent history of symptoms CT was taken. In this study two such doubtful cases were diagnosed by CT paranasal sinuses.

Most of them had bilateral maxillary sinusitis and five had unilateral maxillary sinusitis and one had pan sinusitis.

Similarly cases and controls with history of symptoms of GERD (history of esophageal symptoms, chronic symptoms of acid regurgitation or heart burn and reported use of drugs for the symptoms) were subjected to

(1) Barium esophagogram and

(2) Upper Gastro intestinal endoscopy.

Upper Gastro intestinal endoscopy was performed by pediatric Gastroenterologist of Institute of child health. The test was done on empty stomach without anesthesia. The esophagus and esophago gastric junction, duodenum, stomach, were looked for any pathology.

Those with symptoms with findings of either patulous lower esophageal sphincter with reflux both in anteroflux and retroflux movement, hiatus hernia and findings of esophagitis were diagnosed as having Gastro esophageal reflux disease.

STATISTICAL ANALYSIS

To associate co-morbid conditions (Allergic rhinitis, Sinusitis, GERD) to cases and controls, Odds ratio with 95% confidence interval (OR with 95% C.I) was arrived by univariate analysis.

Multi variate logistic analysis was applied to findout adjusted Odds ratio with 95% confidence interval (adjusted OR with 95% CI).

Statistical analysis was done using SPSS software.

Observation

OBSERVATION

TABLE – 1

SEX DISTRIBUTION IN CHILDREN AGED 6-12 YEARS WITH ASTHMA

Sex	Children with Asthma		Control		Total	
	n	%	n	%	n	%
Female	67	42.1	148	46.5	215	45.1
Male	92	57.9	170	53.5	262	54.9
Total	159	100.0	318	100.0	477	100.0

Of the 159 children with asthma 92 (57.9%) were males and 67 (42.1%) were females.

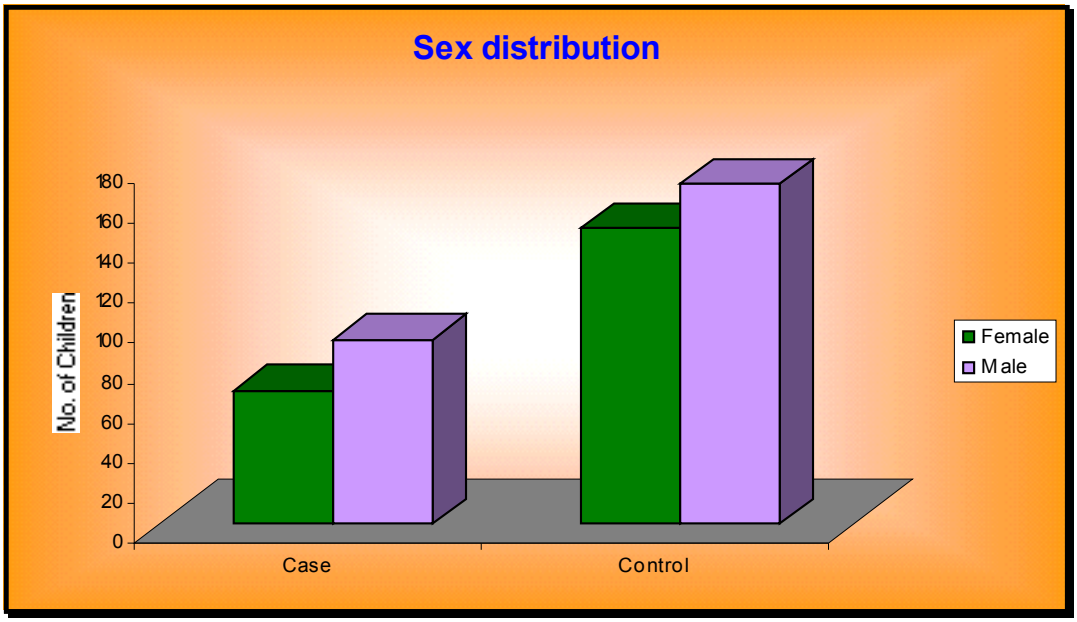

Sex distribution
No. of Children
180
160
140
120
100
80
60
40
20
0
Case
Control
Female
Male

TABLE - 2

AGE DISTRIBUTION IN CHILDREN WITH ASTHMA

Age in years	Children with Asthma		Control		Total	
	n	%	n	%	n	%
6	38	23.9	64	20.1	102	21.4
7	33	20.8	50	15.7	83	17.4
8	24	15.1	51	16.0	75	15.7
9	16	10.1	42	13.2	58	12.2
10	16	10.1	28	8.8	44	9.2
11	18	11.3	44	13.8	62	13.0
12	14	8.8	39	12.3	53	11.1
Total	**159**	**100.0**	**318**	**100.0**	**477**	**100.0**

Most of the children were in the age group of 6 to 8 years.

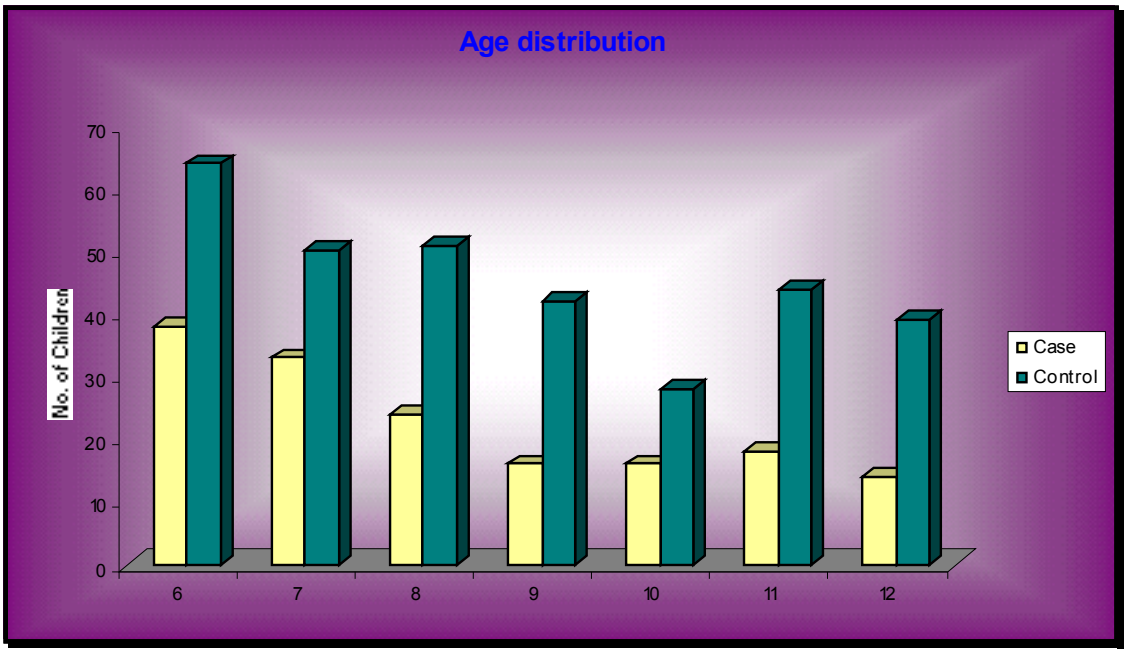

Age distribution
No. of Children
70
60
50
40
30
20
10
0
6
7
8
9
10
11
12
Case
Control

TABLE – 3

CHILDREN WITH ASTHMA AND GRADES OF SEVERITY

Grades of Asthma	Mild Intermittent	Mild Persistent	Moderate Persistent	Severe Persistent	Total
n	42	52	58	7	159
(%)	26.4%	32.7%	36.5%	4.4%	100%

The relative distribution of children with asthma in each grade was observed.

There were :

42 (26.4%) Children in mild intermittent

52(32.7%) Children in mild persistent

58 (36.5%) Children in moderate persistent

7 (4.4%) Children in severe persistent

The prevalence of children with asthma in severe persistent grade was low.

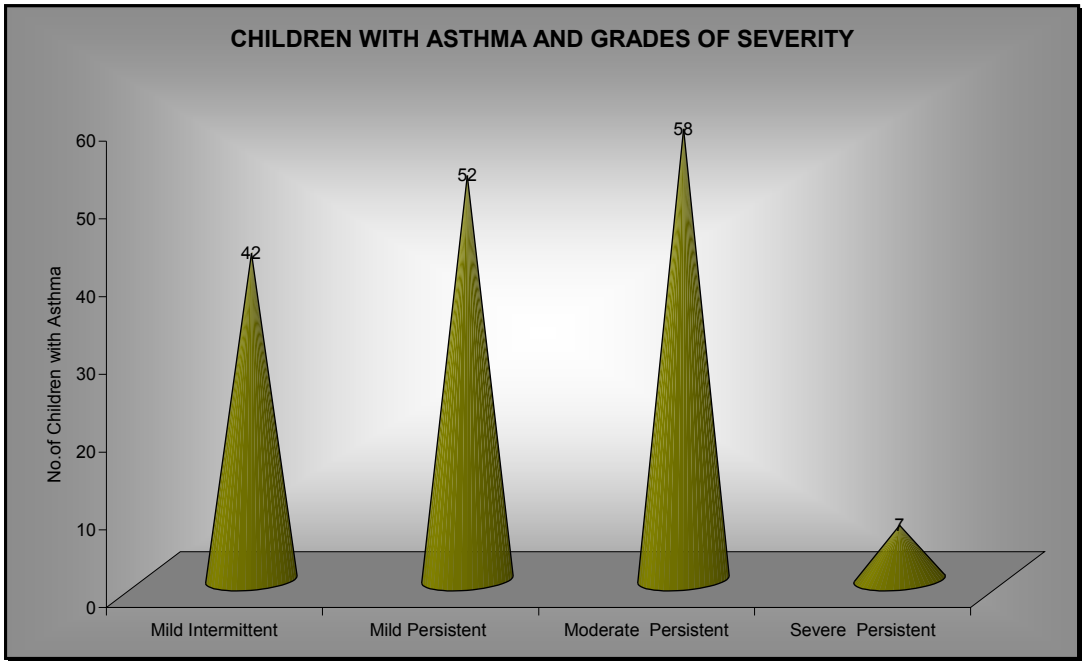

CHILDREN WITH ASTHMA AND GRADES OF SEVERITY
No.of Children with Asthma
60
50
40
30
20
10
0
42
52
58
7
Mild Intermittent
Mild Persistent
Moderate Persistent
Severe Persistent

TABLE – 4

FAMILY HISTORY OF ASTHMA / ATOPY

Grade of asthma	Relationship						Total	
	0		1		2			
	n	%	n	%	n	%	n	%
Mild Intermittent	27	29.0	11	31.4	4	12.9	42	26.4
Mild Persistent	32	34.4	9	25.7	11	35.5	52	32.7
Moderate Persistent	29	31.2	14	40.0	15	48.4	58	36.5
Severe Persistent	5	5.4	1	2.9	1	3.2	7	4.4
Total	**93**	**100.0**	**35**	**100.0**	**31**	**100.0**	**159**	**100.0**

0 – No family history

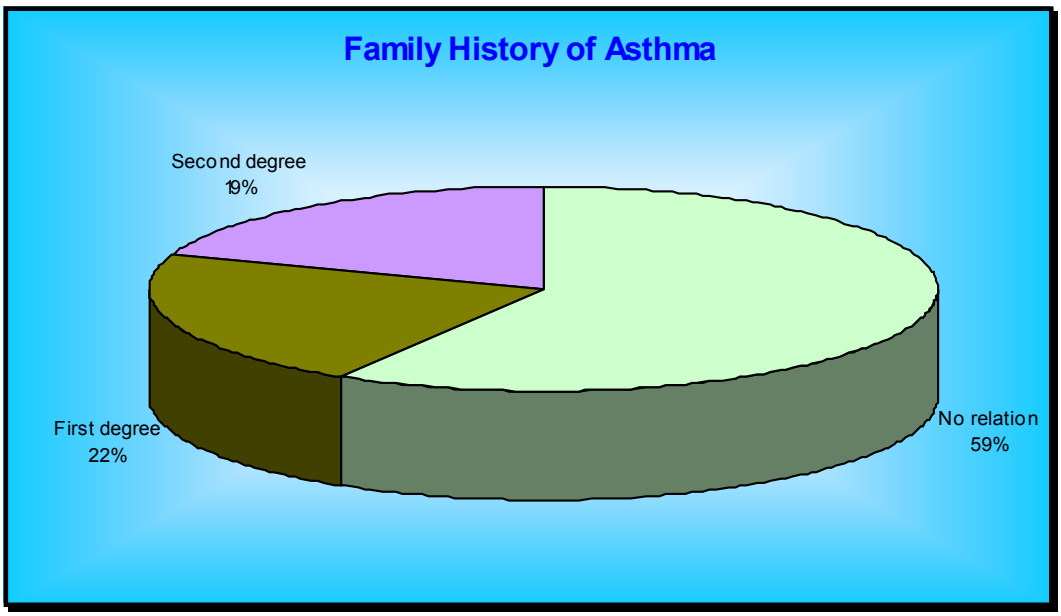
1 – Family history in first degree relative

2 – Family history in second degree relative

Family history of asthma / allergy was observed in 66 children among 159.

Family history of asthma / allergy (in first degree relatives) was seen in 31.4 % in grade 1 asthma, 25.7% in grade 2 asthma, 40% in grade 3 asthma and 2.9% in grade 4 asthma.

Family history of asthma / allergy (in second degree relatives) was seen in 12.9 % in grade 1 asthma, 35.5% in grade 2 asthma, 48.4% in grade 3 asthma and 3.2% in grade 4 asthma.


Family History of Asthma
Second degree
19%
First degree
22%
No relation
59%

CO-MORBID CONDITIONS IN CHILDREN WITH ASTHMA AGAINST CONTROLS - UNIVARIATE ANALYSIS

TABLE – 5.1

ALLERGIC RHINITIS AND ASTHMA

Allergic Rhinitis	Children with asthma n (%)	Control n (%)	OR	95% C.I.		Statistical Significance
				Lower	Upper	
Yes	62 (39.0%)	11 (3.5%)	17.84	8.68	37.48	<0.001
No	97 (61.0%)	307 (96.5%)				
Total	159 (100%)	318 (100%)				

Allergic rhinitis was seen in 39.0% of children with asthma as compared to 3.5% of controls.

Odds of having allergic rhinitis among children with asthma was 17.84 times when compared to children without asthma [OR (95% CI) : 17.84 (8.68 – 37.48)].

TABLE – 5.2

SINUSITIS AND ASTHMA

Sinusitis	Children with asthma n (%)	Control n (%)	OR	95% C.I.		Statistical Significance
				Lower	Upper	
Yes	26 (16.4%)	4 (1.3%)	15.35	4.96	52.95	<0.001
No	133 (83.6%)	314 (98.7%)				
Total	159 (100%)	318 (100%)				

Sinusitis was seen in 16.4% of children with asthma as compared to 1.3% of controls.

Odds of having sinusitis among children with asthma was 15.35 times when compared to children with out asthma. [OR (95% CI) : 15.35 (4.96 - 52.95)].

TABLE – 5.3

GASTROESOPHAGEAL REFLUX AND ASTHMA

GERD	Children with asthma n (%)	Control n (%)	OR	95% C.I.		Statistical Significance
				Lower	Upper	
Yes	9 (5.7%)	6 (1.9%)	3.12	0.99	10.07	Not Significant
No	150 (94.3%)	312 (98.1%)				
Total	159 (100%)	318 (100%)				

GERD was seen in 5.7% of children with asthma as compared to 1.9% of controls.

Eventhough Odds Ratio was 3.12, 95% confidence interval was not achieved. So GERD was not significantly associated with children with asthma.

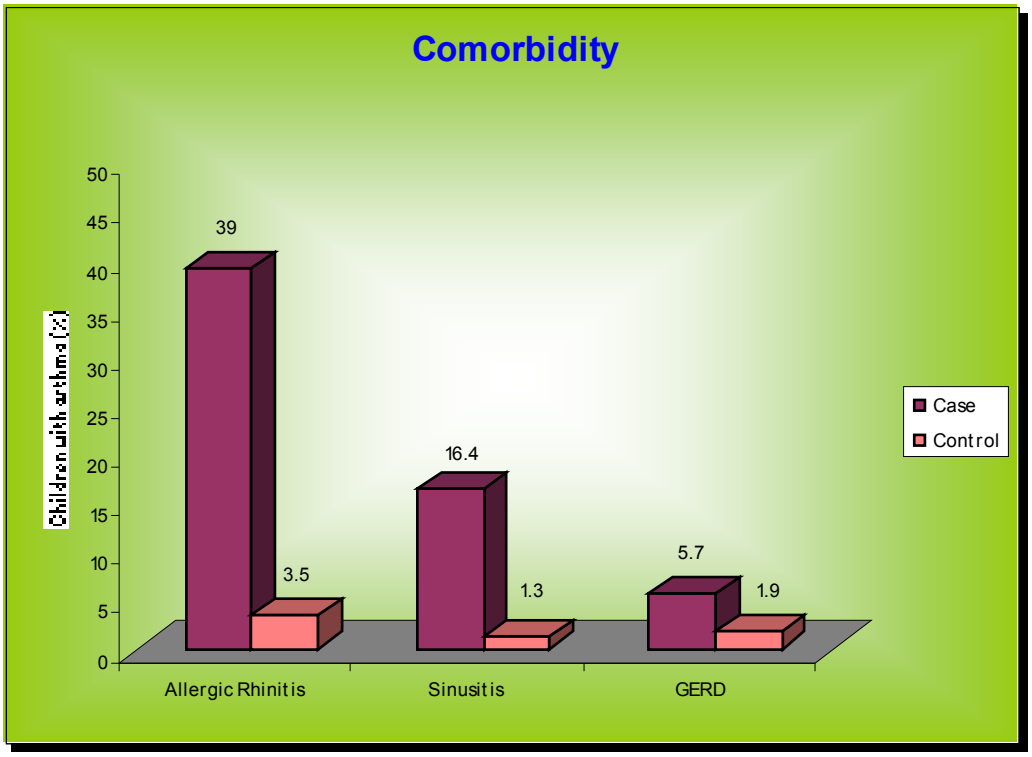

Comorbidity
Children with asthma (%)
50
45
40
35
30
25
20
15
10
5
0
39
3.5
16.4
1.3
5.7
1.9
Allergic Rhinitis
Sinusitis
GERD
Case
Control

TABLE – 6

CO-MORBID CONDITIONS IN CHILDREN WITH ASTHMA AGAINST CONTROLS - MULTIVARIATE ANALYSIS

Comorbid condition	Beta co-efficient	Standard Error	Significance	Adjusted OR	95% Confidence Interval	
					Lower	Upper
Allergic rhinitis	2.976	0.408	0.000	19.608	8.819	43.597
Sinusitis	2.426	0.589	0.000	11.315	3.567	35.887
GERD	-0.932	0.669	0.163	0.394	0.106	1.461

On applying multi variate logistic regression analysis,

Adjusted OR for Allergic rhinitis was 19.608

Adjusted OR for sinusitis was 11.315

Adjusted OR for GERD was 0.394

P-value for Allergic Rhinitis was 0.000 (Significant)

P-value for Sinusitis was 0.000 (Significant)

P-value for GERD was 0.163 (Not significant)

Allergic rhinitis and sinusitis were independently associated with asthma.

TABLE – 7

COMORBID CONDITIONS IN VARIOUS GRADES OF ASTHMA

S.No.	Comorbid condition	Mild intermittent n (%)	Mild persistent n (%)	Moderate persistent n (%)	Severe persistent n (%)	Statistical significance
1.	**Allergic Rhinitis**					
	Yes	8 (19.0%)	19 (36.5%)	31 (53.4%)	4 (57.1%)	
	No	34 (81.0%)	33 (63.5%)	27 (46.6%)	3 (42.9%)	< 0.01
	Total	42 (100.0%)	52 (100.0%)	58 (100.0%)	7 (100.0%)	
2.	**Sinusitis**					
	Yes	3 (7.1%)	6 (11.5%)	17 (29.3%)	0 (0.0%)	
	No	39 (92.9%)	46 (88.5%)	41 (70.7%)	7 (100.0%)	< 0.01
	Total	42 (100.0%)	52 (100.0%)	58 (100.0%)	7 (100.0%)	
3.	**GERD**					
	Yes	0 (0.0%)	2 (3.8%)	6 (10.3%)	1 (14.3%)	
	No	42 (100.0%)	50 (96.2%)	52 (89.7%)	6 (85.7%)	Not significant
	Total	42 (100.0%)	52 (100.0%)	58 (100.0%)	7 (100.0%)	

The co-morbid conditions were seen greater percentage in Grade III & IV.

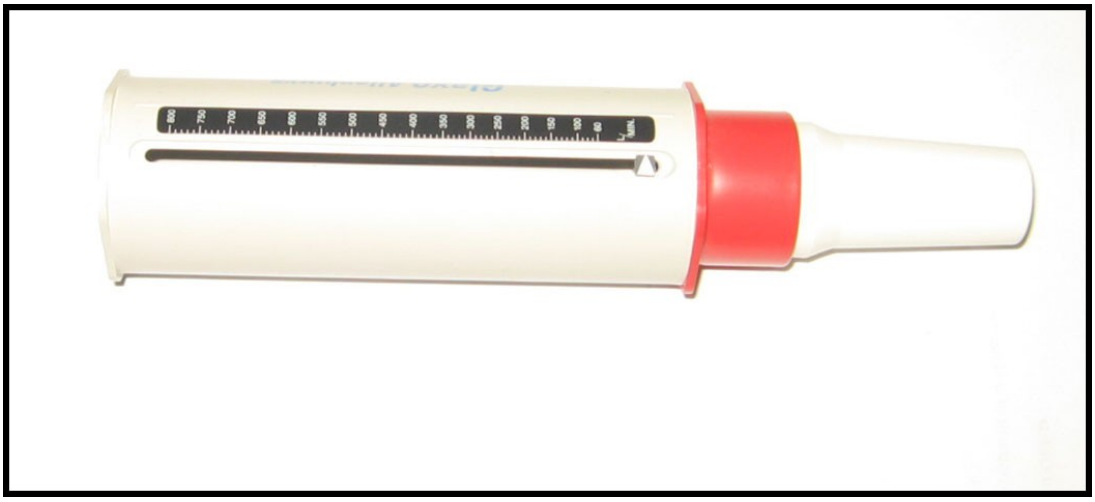
The P value for Allergic rhinitis was < 0.01

The P value for Sinusitis was < 0.01

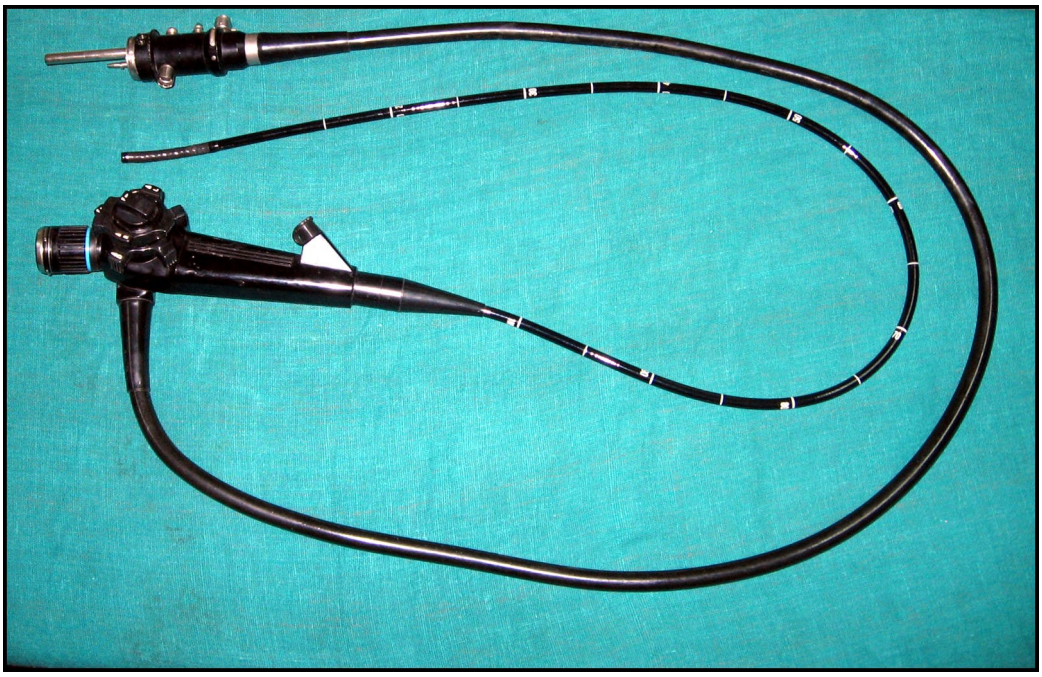
The P value for GERD was not significant.

LUNG FUNCTION TESTS

SPIROMETRY

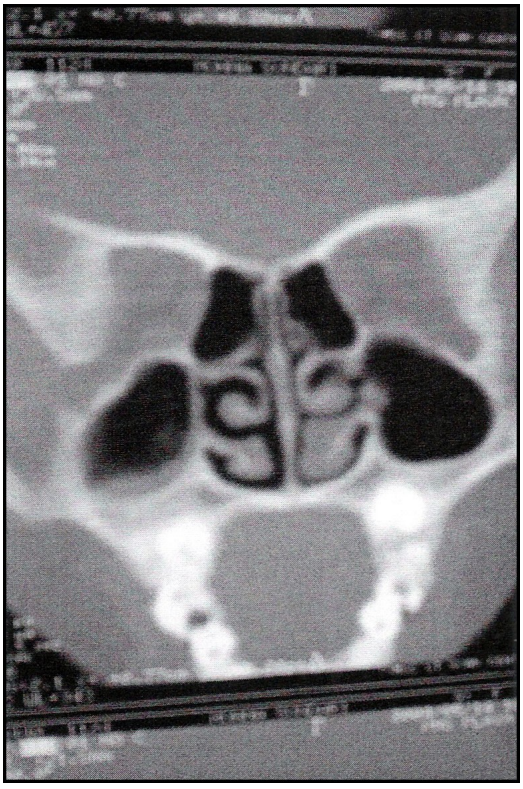


PEAK FLOW METER



UPPER GASTROINTESTINAL ENDOSCOPE

X-RAY WATER'S SHOWING BILATERAL MAXILLARY SINUSITIS



CT SHOWING RIGHT MAXILLARY SINUSITIS

Discussion

DISCUSSION

AGE AND SEX DISTRIBUTION OF ASTHMA

Most of the children with asthma were in the age group of 6-8 years, although they were more or less equally distributed. The male : female ratio is 1.22 : 1, although no statistical significance was found.

FAMILY HISTORY OF ASTHMA / ATOPY

The children with asthma with family History of Asthma / Atopy were 66 out of 159. The distribution of them among first degree and second degree relatives were 35 and 31 respectively. The relationship of family History of asthma/atopy with different grades of asthma was not statistically significant.

But several studies like A.Ten Brinke et al[10]., have shown that patients with frequent asthma exacerbations (Severe asthma) more often had family history of asthma/atopy which was statistically significant.

SEVERITY OF ASTHMA

The distribution of asthma was less in Grade IV (Severe Persistent) - 4.4 %. Several studies including Irwin et al[11], that were done in adult patients with asthma have shown more or less equal distribution among different grades of asthma.

CO-MORBID FACTORS AND ASTHMA

Allergic Rhinitis was more prevalent in asthma and was statistically significant (OR was 17.84 with 95% confidence bounds of 8.68 to 37.48; $P < 0.001$). Sinusitis was also more prevalent in asthma and was statistically significant (OR was 15.35 with 95% confidence bounds of 4.96 to 52.95; $P < 0.001$). Also with multivariate analysis, allergic rhinitis and sinusitis were independently associated with asthma [(Allergic Rhinitis : adjusted OR was 19.608 and P=0.000) and in (sinusitis - adjusted OR was - 11.315 and P= 0.000)]. The prevalence of GERD in asthma was not statistically significant (OR 3.12 and P value - not significant).

This was in accordance with several studies including Ten Brinke et al[12]., Harding S.M. et al[23]., except the prevalence of GERD in asthma.

CO-MORBID FACTORS AND SEVERITY OF ASTHMA

Allergic Rhinitis was prevalent in severe grades of asthma ($P < 0.01$) (i.e., more prevalent in moderate and severe asthma than in mild asthma). Sinusitis, though no cases were in severe persistent asthma, was more prevalent in moderate persistent asthma ($P < 0.01$) than in mild persistent and mild intermittent.

In study by Daniel L. Hamilos, MD et al.[14], sinusitis was found to be independently associated with moderate / severe asthma ($P= 0.032$). GERD was also statistically more significant in moderate / severe group ($P=0.013$). Allergic Rhinitis was also more prevalent in moderate / severe group though statistically not significant (OR is 1.2)

The overall impact of GERD would have been greater if 24 hour esophageal pH manometry which was considered as the Gold standard test was done. This was not feasible in our setup.

Conclusion

CONCLUSION

- This study concludes that the prevalence of Allergic Rhinitis and sinusitis was greater in children with asthma.
- There is a higher prevalence of Allergic rhinitis and sinusitis among moderate /severe asthma than mild group of children with asthma, implicating that these factors could contribute to the severity of asthma and its exacerbations.
- So all the children diagnosed as bronchial asthma, particularly moderate persistent and severe persistent asthma should be evaluated for the presence of co-morbid conditions, which if treated simultaneously will result in less asthma exacerbations with a greater improvement in their quality of life including schooling, sports and recreation.

Recommendation

RECOMMENDATION

All the children with asthma should be subjected to investigation of co-morbid conditions.

Annexure - I

DATA ENTRY CARD

Name : Age : Sex :

Address : Environment :

Height : Weight :

History of Recurrent Wheeze :

History of Recurrent Isolated cough :

History of Recurrent Breathlessness :

History of Nocturnal Cough :

History of Tightness of Chest :

History of Atopy :

History of Trigger Induced Symptoms :

History of Activity/ Exercise Induced

Symptoms :

History of seasonal Exacerbations :

Family History of Allergic diathesis :

Peak expiratory flow rate :

Diurnal Variation in PEFR :

History of allergic Rhinitis

Paroxysmal sneezing :

Nasal obstruction :

Itching :

Rhinorrhea :

History of sinusitis

Facial pain on pressure :

Headache :

Nasal Purulence or Discharge :

Hyposmia or Anosmia :

Pain, Fever, Halitosis :

Upper respiratory

symptoms for 7-10 Days :

History of GERD

Chronic symptoms of acid regurgitation :

Heart burn :

Vomiting :

Reported use of drugs for the symptoms :

CLINICAL EXAMINATION

Day symptoms	Night symptoms	PEFR % of expected value	Severity Grade

INVESTIGATIONS :

Haemoglobin :

Total Count :

Differential Count :

Mantoux :

Chest X-ray :

Spirometry :

Anterior Rhinoscopy :

Nasal mucosal smear for eoxinophills :

X-ray paranasal sinuses :

Nasal scopy :

Barium esophagogram :

Upper Gastrointestinal Endoscopy :

Annexure - II

BIBLIOGRAPHY

1. Beasley R. et al., prevalence and etiology of asthma J. Allergy Clin. Immunol., 200; 105, 5466-72.

2. Martinez RD et al. Asthma and wheezing in the first 6 years of life. The group health medical Associates N ENG J. Med. 1995, 332(3) : 133-8.

3. CIBA Guest Symposium. Terminology, definitions and classifications of chronic pulmonary emphysema and related condition. Thorax 1959 : 280-99.

4. American thoracic society. Definitions and classifications of chronic Bronchitis; asthma and pulmonary emphayseam Am. Rev. Respir. Dis., 1962; 85 : 762-8.

5. Therasa Guilbest et al., National History of asthma in : Pediatric asthma pediair Clin. N. Am 50 (2003) 523 – 538.

6. National Institute of Health, Bethesda, MD: National Heart lung and Blood Institute. National Asthma Education and prevention programme: Export Panel Report 2 : Guidelines for diagnosis and management of Asthma 2002.

7. Asthma By consensus IAP respiratory chapter section 1 and 2.

8. Masoli.M et al., the Global burden of asthma. GINA Dissemination committee report Allergy 2004;59;

9. Nelsons textbook of Pediatrics 17th edition 2004 765,749,750,767,759, 762, 763.

10. Ten Brinke.A. et al., - Factors associated with frequent exacerbations in patients with severe asthma-Gibson's text book of chest medicine.

11. Irwin RS., curley. FJ, et al., difficult to control asthma – contributive factors and out come of systematic management protocol.

12. Ten Brinke A, Zwinderman AL, et al., factors associated with persistent air flow limitation in severe asthma.

13. Bosquet J, Van cauwen berge P, Khaltaeve N, Allergic rhinitis and its im pact on asthma. Workshop report in colloboration with WORLD HEALTH ORGANISATION (ARIA) J. Allergy clin Immunol 2001; 108;5 (2) 147.

14. Daniel L. Hamilos, MD – causative and contributive factors to asthma se verity (Chest 2003; 124: 1781-88).

15. Bresciani M. et al., Rhinosinusitis in severe asthma J.Allergy clin Immuol 2001 Jan 107 (1) 73 – 80.

16. Elias Hernandez MT. et al., Risk factors for bronchial asthma in patients with rhinitis. Arch Broncho Pneumol. 2001 Nov.

17. Corren J. et al., Rhinitis therapy and the prevention of hospital care for asthma a case control study. J. Allergy Clin Immurol 2004 Mars 113 (3) 415 – 9

18. 14. Tosca M.A et al., Ann allergy asthma immunol 2003 Jul; 91 (1) 71–8 Improvement of clinical and immuno pathological parameters in asthmatic children treated for concomitant Rhino sinusitis.

19. Fontanarri P, et al. : Changes in airway resistance induced by nasal inhibitor of cold dry, dry or moist air in normal individuals. J. Appl. Physiol., 81 : 1739, 1996.

20. Kaufman J, et al., : The effect of trigemmal resection on reflex broncho constriction after nasal and nasopharyngeal irritation on airway resistance in man. Am. Rev. Respir. Dis. 100 : 626, 1969.

21. Mc Laurin JG : Chest complications of sinus disease. Ann Otol Rhinol Laryngol. 41 : 780.

22. Mullen WV, Wyder CT : Experimental Lesions of lung produced by the inhalation of fluid from the nose and throat. Am. Rev. Tuberc. 4 : 6840, 1920.

23. Harding, SM, Richter, JE. et al., The role of Gastro esophageal reflux in chronic cough and asthma. Chest 1997; 111 1389 – 1402.

24. Slavin, RG et al., relationship of Nasal disease and sinusitis to bronchial asthma. Ann allergy 1982; 49,7-79

25. Rachelefsky, GS, Katz, RM, Siegel, SS chronic sinus disease with associated reactive airway disease in children. Pediatrics 1984 ; 73 : 526-529.

26. Rolla, G, Colagrende, et al., Damage of pharyngeal mucosa and hyper responsiveness of airway in sinusitis. J. Allergy Clin Immunol 1997; 100, 52 – 57

27. M.Mc Geehan, W.W. Busse 1 med clin N Am 86 (2002) 1073 – 1090 - GERD and Rhino Sinusitis with Asthma.

28. Casale TB et al., Immunology asthma and Rhinitis: Pathogenetic factors and therepeutic options A M J respir unit care red 1997 : 160.

29. Friedman R.Acterman M.Wald F et al., Asthma and Bacterial sinusitis in children. J. Allergy Clin Immunol 1984: 74 (2) : 185 – 9.

30. Pfister R. et al Screening for sinus disease in patients with asthma. J. Allergy with Immunol 1994 Nov: 94(5) : 804 – 9

31. Bochenska et al., Prevalence of gastro esophageal reflux disease in patients with asthma polmerkurius 2 1 ek 2004 Jun; 16 (96): 527 – 31.

32. Buscino L et al., clinical and therapeutic aspects of sinusitis in asthmatic children.

33. Hamilos, DL et al., Gastso esophageal reflux and sinusitis in asthma Clin Chest Med 1995; 16,683-697.

34. Flores. F. et al., Gasteo esophageal reflux in pediatric patients with asthma.

35. JL Mathew , M. Sing and SK Mittal Gasteo esophageal reflux and bronchial asthma – review Post graduate medical journal 2004; 80: 701-705

36. R.E. Miller, J.L Paradise, G.A. Friday P. Fireman and D. Voith the nasal smear for eosinophils in children with allergic rhinitis.

37. Crobach MJ. Hermans J; Diagnosis of allergic rhinitis. Br J Gen pract 46:437, 1996.

38. Mullarkey MF, Webb DR: Allergic and no allergic rhinitis : Their characterization with attention to the meaning of Nasal eosinophilia. J Allergy Clin Immunol 65:122-126,1980.

39. Virant FS., Shapiro GG: Medical management of sinusitis in children.

40. Lanza, DC., Kennedy, DW Rhinosinusitis defined oto laryngol Head neck Surg 1997; 117, S1-S7.

41. Kraft M. the role of bacterial infections in asthma Clin. Chest Med. 2000;21:301-313.

42. Gibson PG., Henry RL., Constilan JL. Gastro-esophageal reflux treatment for asthma in adults and children. Conchrane Database Sys Rev. 2003; 2.

43. Adams RJ, Futilbrigge AL, et al., intranasal steroids and the risk of emergency visits for asthma J. Allergy Clin. Immunol. 2002.

44. Senior BA., Kennedy DW. management of sinusitis in the asthmatic patient. Ann allergy asthma immunol.

45. Vincent D. John Jonathan AM, Leport J., et.al., Gastro esophageal reglux prevalence and relationship with bronchial reactivity in asthma Eur Respir J 1997; 10 : 2255-9.

46. Gustafsson PM, Kjellman Nim, Tibling L. A trial of ranitidine in asthmatic children and adolescents with or without gastro esophageal reflux. Eur Respir J 1992; 5: 201-6.

47. Kiljander TO., Salomaa ER, et.al., Gastro esophageal reflux in asthmotics chest 1999; 116: 1257-64.

48. Mansfield LE., Stein MR., Gastro esophageal reflux and asthma. Ann Allergy. 1981:41:224-226.

49. Vikram Khochoo, MD, et al., Role of Gastro esophageal reflux in older children with persistent asthma. CHEST 2003; 123 : 1008-1013.

50. Huang JL. et al., sinusitis and bronchial asthma in children. Zhoghua Min Guo Xiao Er Key Yi Xue Hui ZaZhi 1995. Jan – Feb. 36 (1) : 20-3.

51. Ferrante ME et al., prevalence of sinusitis in young asthmatics and its relation to bronchial asthma. Mil. Med., 1998 Mar; 163(3) : 180-3.

52. Krajewski Z. et al., prevalence of nasal sinusitis in children with bronchial asthma Pneumonol alergol Po. 1997; 65 Suppl. 1:40-3.

53. Marney SR. Jr. Pathophysiology of reactive airway disease and Sinusitis. Department of medicine Vanderbilt University Medical Center, Nashville, Tennessee USA. Ann. Otol. Rhinol. Laryngol. 1996, Feb : 105(2) : 98-100.